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Improving the Prediction of Cardiac Surgery–Associated Acute Kidney Injury

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Introduction: Acute kidney injury (AKI) is a potentially fatal complication of cardiac surgery. The inability to predict cardiac surgery-associated AKI is a major barrier to prevention and early treatment. Current clinical risk models for the prediction of cardiac surgery-associated AKI are insufficient, particularly in patients with preexisting kidney dysfunction.

Methods: To identify intraoperative variables that might improve the performance of a validated clinical risk score (Cleveland Clinic Score, CCS) for the prediction of cardiac surgery-associated AKI, we conducted a prospective cohort study in 289 consecutive elective cardiac surgery patients at a tertiary care center. We compared the area under the receiver operator characteristic curve (AUC) of a base model including only the CCS with models containing additional selected intraoperative variables including mean arterial pressure, hematocrit, duration of procedure, blood transfusions, and fluid balance. AKI was defined by the Kidney Disease Improving Global Outcomes 2012 criteria.

Results: The CCS alone gave an AUC of 0.72 (95% confidence interval, 0.62–0.82) for postoperative AKI. Nadir intraoperative hematocrit was the only variable that improved AUC for postoperative AKI when added to the CCS (AUC = 0.78; 95% confidence interval, 0.70–0.87; $P = 0.002$). In the subcohort of patients without preexisting chronic kidney disease (n = 214), where the CCS underperformed (AUC, 0.60 [0.43–0.76]), the improvement with the addition of nadir hematocrit was more marked (AUC, 0.74 [0.62–0.86]). Other variables did not improve discrimination.

Discussion: Nadir intraoperative hematocrit is useful in improving discrimination of clinical risk scores for AKI, and may provide a target for intervention.

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Acute kidney injury (AKI) is an important complication of cardiac surgery and is associated with significantly increased morbidity,[1–4] mortality,[1,2,4–10] and health care costs.[5] AKI occurs in up to 18% of patients undergoing cardiac surgery, with 2% of all patients requiring renal replacement therapy.[4] Although overall mortality for cardiac surgery is typically between 2% and 3%,[6,11] this rate doubles with even mild postoperative AKI, and approaches 60% for AKI severe enough to require dialysis.[5–10,12] In addition, cardiac surgery-associated AKI (CSA-AKI) is associated with increased rates of infection,[13] dysfunction in multiple other organ systems,[2–4,14] longer ICU and hospital length of stay,[2] and long-term kidney disease.[1]

CSA-AKI is believed to originate intraoperatively,[15] the cumulative result of ischemic insults,[15–19] systemic inflammation,[20–23] and oxidative stress,[17,22,24,25] ultimately resulting in progression to tubular necrosis. Animal models consistently demonstrate the potential to abrogate or prevent AKI with a variety of pharmaceutical approaches targeting these mechanisms,[26–30] provided the treatment is instituted before significant tubular cell death occurs.[15] In the context of CSA-AKI, for example, the application of this early treatment paradigm requires diagnosis and treatment of AKI intraoperatively, at the time of the incipient injury.[31–34] Unfortunately, timely intraoperative diagnosis of AKI is not yet feasible. Serum creatinine, the

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current standard for AKI diagnosis, takes several days to reach diagnostic thresholds.[34] Even novel urinary biomarkers lack adequate discrimination to guide therapy when measured intraoperatively.[35]

An alternative approach to "real-time" diagnosis is to use clinical variables measured before or at the time of surgery to predict risk of postoperative AKI. Provided the risk model is sufficiently accurate, such a prediction tool could be used to guide the implementation of more intensive renoprotective efforts and surveillance in patients at highest risk. Importantly, better risk prediction could improve pretest probabilities for novel diagnostic tests of CSA-AKI, thereby improving the performance of early diagnostic markers and possibly paving the way for more specific, targeted therapies. A number of predictive models based on preoperative risk factors[9,35–40] have been developed for CSA-AKI. Of these, the Cleveland Clinic Score (CCS, often called the Thakar score) is the best validated and most predictive of these tools (Table 1).[41] Originally developed to predict renal replacement therapy after cardiac surgery, the CCS has since been validated for the prediction of less severe CSA-AKI.[36–38]

Despite its usefulness, the CCS does not incorporate potentially useful intraoperative information. The score is also heavily influenced by preoperative kidney dysfunction, and is less discriminatory in patients with normal preoperative kidney function. We hypothesized that the performance of the CCS could be improved by the incorporation of easily measured intraoperative variables capturing the aspects of adequacy of organ perfusion, such as intraoperative blood pressure, hematocrit, urine output, blood transfusion, and fluid administration.

Table 1. Cleveland Clinic Score

Risk factor	Points
Female gender	1
Congestive heart failure	1
Left ventricular ejection fraction <35%	1
Preoperative use of intra-aortic balloon pump	2
Chronic obstructive pulmonary disease	1
Insulin-requiring diabetes	1
Previous cardiac surgery	1
Emergency surgery	2
Surgery type:	
Coronary artery bypass grafting only	0
Valve repair/replacement only	1
Coronary artery bypass grafting + valve	2
Any other cardiac surgery	2
Preoperative creatinine:	
107 to <186 μM (1.2 to <2.1 mg/dl)	2
≥186 μM (≥2.1 mg/dl)	5
Maximum score	17

METHODS

The University of Manitoba Human Research Ethics Board and the Saint Boniface General Hospital Research Review Committee approved our research protocol, and all patients provided informed consent.

Study Design

We employed an observational prospective cohort design. All adult patients scheduled for elective cardiac surgery at a tertiary care center (Saint Boniface General Hospital, Winnipeg, Canada) were considered for inclusion. Patient recruitment occurred between June 2012 and July 2014. Exclusion criteria included age < 18 years, chronic kidney disease of stage V or greater (Modification of Diet in Renal Disease estimated glomerular filtration rate < 15 ml/min per 1.73 m^2), currently on dialysis for any indication, previous kidney transplant, or planned off-pump procedure.

Data Collection

Data were abstracted from patient charts as well as from the Manitoba Cardiac Surgery Database for the duration of hospital stay from time of entry to the operating room to hospital discharge. All data were collected according to routine clinical practice. Baseline data and demographics were recorded during the presurgical clinic visit and/or on admission to hospital. Mean arterial pressure (MAP) was monitored via an arterial catheter and recorded by the anesthetist at 5-minute intervals. Data on hematocrit from intraoperative arterial blood gas panels were abstracted at the following times: (i) at time of arterial line placement, (ii) on initiation of cardiopulmonary bypass (CPB), (iii) 1 hour after the commencement of CPB, and (iv) at arrival to postoperative ICU. Surgery duration was recorded in the intraoperative record. Pump time and cross clamp time were recorded in the perfusion record. Use of blood products was recorded in a transfusion log. Volume inputs were recorded by the anesthesiologist and perfusionist. Urine outputs for the entire operative period as well as outputs specific to the period while on CPB were recorded intraoperatively by nursing staff. Creatinine was measured at arrival to ICU and in the morning of each postoperative day, along with other routine bloodwork.

Primary Exposure Variables of Interest

The CCS, a well-validated AKI risk score, was calculated based on the relevant preoperative variables for each patient (Table 1). Nadir hematocrit was defined as the lowest of the 4 hematocrits measured during the operation at the time points described above. Average MAP was defined as the average of all MAP readings recorded during surgery. The total number of

transfusions given during surgery and pump time were abstracted from the perfusionists' records. Average hourly urine output during surgery was calculated by dividing the total intraoperative urine volume by the duration of the surgery.

Primary Outcome

AKI was defined according to the 2012 KDIGO guidelines (rise in serum creatinine $\geq$ 26.5 μM within 48 hours, or serum creatinine $\geq$ 150% baseline within 7 days). We did not include the oliguria criteria in our definition of CSA-AKI. Urine output after cardiac surgery is a reflection of many parameters apart from renal damage (e.g., fluid balance, diuretic use, altered renin-angiotensin-aldosterone axis), and so is generally considered to be unhelpful in identifying CSA-AKI after cardiac surgery.[51,52]

Statistical Analyses

SAS version 9.3 was used for all statistical analyses.

Main Analysis

From a clinical perspective, the added complexity of monitoring and incorporating intraoperative information can only be justified if that information significantly improves AKI prediction beyond current prediction models. The CCS is a widely used and well-validated clinical AKI prediction model, and was used as our reference model in all analyses. We first generated a logistic regression model incorporating only the CCS. We then sequentially added candidate intraoperative variables to the base model. Variables were retained in the model only if they significantly improved the *c*-statistic of the base CCS model. Although the *c*-statistic was our primary metric of model performance, we also examined alternative measures of model discrimination (integrated discrimination improvement), as well as model calibration (Hosmer-Lemeshow) and reclassification in the final models.[53,54]

Secondary Analysis

The CCS is heavily influenced by preoperative kidney dysfunction, and may perform less well in patients without prior kidney dysfunction. We therefore examined the performance of the CCS, with and without the addition of preoperative variables, in a subcohort of individuals without kidney dysfunction at baseline, defined as an estimated glomerular filtration rate $\geq$ 60 ml/min.

Sensitivity Analyses

We conducted several sensitivity analyses to explore whether different thresholds applied to each of the main variables tested might alter the models (Supplementary Table S1).

RESULTS

Study Population

Demographic and operative data for the prospective cohort of 289 consecutive adult elective cardiac surgery patients are presented in Figure 1 and Table 2. All patients were followed until discharge from hospital. The cohort was predominantly male, with an average age of 66 years. As expected, risk factors for heart disease were prevalent, including hypertension (71%), diabetes mellitus (32%), and history of myocardial infarction (36%). New CSA-AKI occurred in 12% (n = 35) of the study cohort overall, and in 7.5% (n = 16) in the subgroup without prior kidney dysfunction. Patients who developed AKI as defined by the 2012 KDIGO criteria had lower preoperative Modification of Diet in Renal Disease estimated glomerular filtration rate and were more likely to be diabetic and have a history of congestive heart failure. Not surprisingly, those who developed AKI were sicker than those who did not, with a higher score on the European System for Cardiac Operative Risk Evaluation (euroSCORE II; 4.0 vs. 2.6 in AKI vs. non-AKI, respectively). The euroSCORE II is a widely used predictive model for mortality after cardiac surgery and is based on preoperative health status and type of surgery.[42] Similar trends in demographic and operative variables were observed in the subgroup of patients without prior kidney dysfunction (Table 3).

Patients who developed CSA-AKI had a higher mean CCS of 3.3, compared with a mean of 1.8 in those who did not. This is in keeping with the previous literature for elective (nonemergent) cardiac surgery cohorts.[9,37–39]

Intraoperative Variables

We examined the univariate association between selected intraoperative variables and AKI status (Table 4). CPB time was longer in those developing AKI (125 vs. 107 minutes); however, intraoperative urine

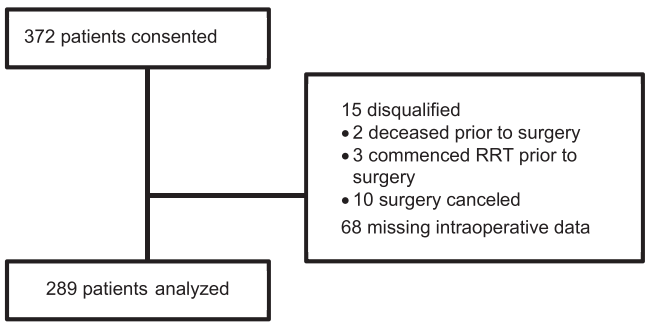

Figure 1. STROBE diagram of cohort. RRT, renal replacement therapy.

Table 2. Selected baseline characteristics of the full cohort

	Total	Non-AKI	AKI	P
N	289	254	35	
Age (yr)	66 (10)	66 (10)	69 (11)	0.05*
Female (%)	24	23	31	0.3
Previous CABG (%)	3.1	2.8	5.7	0.3
Previous cardiac intervention (%)	10	10	14	0.4
Comorbid conditions (%)				
Diabetes mellitus	32	29	57	0.002*
COPD	7.2	7.5	5.7	1.0
Heart failure	9.3	7.5	23	0.008*
Myocardial infarction	36	37	31	0.6
Arrhythmia	19	17	31	0.06
Hypertension	71	70	83	0.1
ICD	2.4	2.0	5.7	0.2
Peripheral artery disease	7.9	7.1	14	0.2
Cerebrovascular accident	5.9	5.1	11	0.1
Transient ischemic attack	4.1	4.3	2.9	1.0
Type of surgery (% CABG only)	61	63	54	0.4
EuroSCORE II	2.7 (3.8)	2.5 (3.8)	4.0 (3.3)	0.03*
CCS	2.0 (1.7)	1.8 (1.5)	3.3 (2.1)	<0.001
Presurgery kidney function				
Baseline serum creatinine (μmol/l)	92 (33)	89 (27)	120 (52)	<0.0001*
eGFR (ml/min per 1.73 m^2)	78 (23)	81 (22)	60 (21)	<0.0001*

CABG, coronary artery bypass grafting; CCS, Cleveland Clinic Score; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator.
*Significant at $P < 0.05$.

output and MAP were similar in both groups. Patients with AKI exhibited a lower nadir hematocrit (defined as the lowest hematocrit observed during intraoperative sampling) than those without AKI

Table 3. Selected baseline characteristics of patients without prior CKD

	Total	Non-AKI	AKI	P
No.	214	198	16	
Age (yr)	65 (10)	65 (910)	69 (13)	0.04*
Female (%)	24	23	38	0.2
Previous CABG (%)	2.4	2.5	0.0	1.0
Previous cardiac intervention (%)	8.5	8.2	12	0.6
Comorbid conditions (%)				
Diabetes mellitus	28	27	38	0.4
COPD	8.4	8.1	12	0.6
Heart failure	5.6	5.6	6.3	1.0
Myocardial infarction	34	35	25	0.4
Arrhythmia	17	15	31	0.2
Hypertension	67	67	69	0.9
ICD	1.4	1.0	6.3	0.2
Peripheral artery disease	6.1	6.1	6.3	1.0
Cerebrovascular accident	2.8	2.5	6.3	0.4
Transient ischemic attack	3.8	3.6	6.3	0.5
Type of surgery (% CABG only)	63	63	56	0.6
EuroSCORE II	2.0 (2.5)	2.0 (2.5)	3.0 (2.9)	0.1
Thakar score	1.3 (1.1)	1.3 (1.1)	1.8 (1.4)	0.2
Presurgery kidney function				
Baseline serum creatinine (μmol/l)	78 (14)	78 (14)	82 (14)	0.4
eGFR (ml/min per 1.73 m^2)	88 (17)	89 (17)	79 (11)	0.02*

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator.
*Significant at $P < 0.05$.

Table 4. Association between selected intraoperative variables and AKI

Intraoperative variable	Overall	Non-AKI	AKI	P
Pump time (min)	109 (49)	107 (48)	125 (54)	0.04
Nadir hematocrit		0.28 (0.04)	0.25 (0.03)	<0.001
Total urine output in OR (ml)	783 (471)	794 (481)	699 (382)	0.3
Average MAP (mm Hg)	71.2 (4.6)	71.2 (4.6)	71.3 (4.9)	0.9
Total crystalloid in OR (ml)	4698 (1294)	4641 (1264)	5113 (1424)	0.04
Total PRBC in OR (units)	0.71 (1.57)	0.60 (1.44)	1.51 (2.13)	0.001

AKI, acute kidney injury; MAP, mean arterial pressure; OR, operating room; PRBC, packed red blood cells.

(0.25 ± 0.03 vs. 0.28 ± 0.04; $P < 0.001$). Total crystalloid administered was slightly greater in patients who developed AKI (5113 ± 1424 vs. 4641 ± 1264; $P = 0.04$), as was the total number of units of packed red blood cells transfused (1.51 ± 2.13 vs. 0.60 ± 1.44; $P = 0.001$). Results were similar among patients without CKD before surgery (Table 5).

Effect of Intraoperative Variables on Prediction

The CCS alone showed reasonable discrimination for AKI (*c*-statistic 0.72 [95% confidence interval, 0.62–0.82]; Table 6).

Nadir hematocrit was the only variable conferring significant improvement in discrimination (Figure 2, *c*-statistic 0.78 [0.70–0.87], $P = 0.002$, compared with CCS alone). This model had acceptable calibration (Supplementary Table S1), and led to significant integrated discrimination improvement relative to the CCS alone. The category-free net reclassification improvement was 58.8% (24.7%–92.8%), $P = 0.001$, indicating significant overall improvement in risk classification.

In contrast, duration of bypass, MAP, transfusion, and intraoperative urine output did not improve AKI discrimination beyond that achieved by the CCS alone.

In a secondary analysis, we restricted our analysis to the subcohort of patients without known kidney disease before surgery (n = 214; Table 7 and Figure 3). Discrimination of the CCS alone in this subgroup was poor (0.60 [0.43–0.76]). Nadir hematocrit significantly improved model discrimination (0.74 [0.62–0.86]). None of the other variables significantly improved discrimination of the CCS.

Table 5. Association between selected intraoperative variables and AKI in patients without prior CKD

Intraoperative variable	Total	Non-AKI	AKI	P
Pump time (min)	106 (44)	105 (43)	126 (52)	0.102
Nadir hematocrit	0.29 (0.04)	0.29 (0.04)	0.25 (0.04)	0.001
Total urine output in OR (ml)	808 (484)	808 (493)	804 (371)	0.726
Average MAP (mm Hg)	71.1 (4.5)	71.2 (4.6)	70.5 (4.3)	0.661
Total crystalloid in OR (ml)	4592 (1247)	4542 (1227)	5217 (1368)	0.044
Total PRBC in OR (units)	0.61 (1.53)	0.53 (1.46)	1.69 (1.99)	<0.001

AKI, acute kidney injury; CKD, chronic kidney disease; MAP, mean arterial pressure; OR, operating room; PRBC, packed red blood cells.

Table 6. Change in model discrimination for AKI with the addition of selected intraoperative variables to the Cleveland Clinic Score (CCS) alone: full cohort (n = 289)

Model	Area under the ROC curve	95% CI	*P* value (compared with Thakar only)
CCS (base model)	0.72	0.62–0.82	Reference model
CCS + Pump Time	0.73	0.62–0.83	0.4
CCS + Total Volume Input	0.73	0.62–0.83	0.5
CCS + Red Blood Cell Transfusion	0.75	0.65–0.85	0.07
CCS + Hematocrit Nadir	**0.78**	**0.70–0.87**	**0.002**
CCS + Average MAP	0.72	0.62–0.83	0.8
CCS + Average Urine Output/h in OR	0.73	0.63–0.83	0.4

AKI, acute kidney injury; CI, confidence interval; MAP, mean arterial pressure; OR, operating room; ROC, receiver operator characteristic.

Table 7. Change in model discrimination for AKI with the addition of selected intraoperative variables to the Cleveland Clinic Score (CCS): subcohort without prior CKD (n = 214)

Model	Area under the ROC curve	95% CI	*P* value (compared with Thakar alone)
CCS (base model)	0.60	0.43–0.76	Reference
CCS + Pump Time	0.61	0.46–0.76	0.7
CCS + Total Volume Input	0.65	0.49–0.81	0.3
CCS + Red Blood Cell Transfusion	0.68	0.51–0.85	0.07
CCS + Hematocrit Nadir	**0.74**	**0.62–0.86**	**0.01**
CCS + Average MAP	0.61	0.45–0.76	0.8
CCS + Average Urine Output/h in OR	0.62	0.47–0.77	0.4

Pump Time: total duration of CPB. Total Volume Input: fluid volume given during OR time. Red Blood Cell Transfusion: whether or not transfusion of RBC was given, regardless of amount. Hematocrit Nadir: lowest intraoperative hematocrit. Average MAP: mean of intraoperative MAP measurements. Average Urine Output/h in OR: total urine output measured during OR/duration of OR.
AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; MAP, mean arterial pressure; OR, operating room; RBC, red blood cell; ROC, receiver operator characteristic.

Sensitivity Analyses

In a set of sensitivity analyses, alternative methods of defining the primary intraoperative exposure variables were explored (SDC, Table 1). As with the main analysis, nadir hematocrit remained the most predictive intraoperative variable. Hematocrit at the start of CPB or at 1 hour into CPB also appeared to improve discrimination, but to a lesser extent than nadir hematocrit. Of note, hematocrit at arrival to the operating room did not improve prediction. Prolonged hypotension, specifically a MAP < 55 mm Hg for more than 25 minutes, appeared to confer an additional small increment in discrimination to the base CCS model. The effects of both hematocrit and prolonged hypotension were also seen in the subcohort without kidney disease preoperatively.

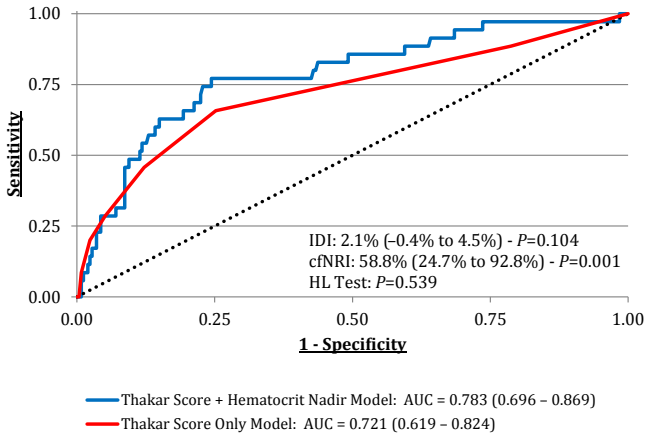

Figure 2. Comparison of area under the curve (AUC) for the receiver operator characteristic curves for the Cleveland Clinic Score (Thakar score) only and the Cleveland Clinic Score (Thakar score) + hematocrit nadir in the full cohort (n = 289). cfNRI, category-free net reclassification index; HL, Hosmer Lemeshow test; IDI, integrated discrimination improvement.

DISCUSSION

In our study of 289 adults undergoing cardiac surgery, we found that the addition of intraoperative nadir hematocrit to a well-established preoperative risk score significantly improved the prediction of new postoperative AKI. The improvement was even more pronounced in patients without CKD, a subgroup where the CCS underperforms. In contrast, intraoperative MAP, crystalloid and blood product administration, and urine output did not improve the prediction of AKI.

Our main finding that measurement of nadir hematocrit improves the prediction of CSA-AKI is in line with recent reports showing that nadir hemoglobin and anemia are important predictors of CSA-AKI.[18,43–45] Prior studies have shown an inverse correlation between nadir intraoperative hematocrit and risk of CSA-AKI in univariate analyses. Our study provides a more robust confirmation of this finding by demonstrating the additive value of nadir hematocrit in a multivariate prediction model. In contrast to previous studies,[44,45] the addition of hematocrit at arrival to the operating room to the CCS did not improve the prediction of AKI in this analysis. This suggests that nadir intraoperative hematocrit is not just a surrogate for preoperative anemia, but adds important new information about AKI risk during the surgical procedure.

The data from this study confirm that the CCS underperformed in patients without preexisting kidney disease. As the CCS weighs the presence or absence of baseline kidney dysfunction quite heavily, awarding 2 points for a serum creatinine of 107 to <186 μM (1.2 to <2.1 mg/dl) and 5 points for a serum creatinine ≥ 186 μM (2.1 mg/dl), this observation is not unexpected.

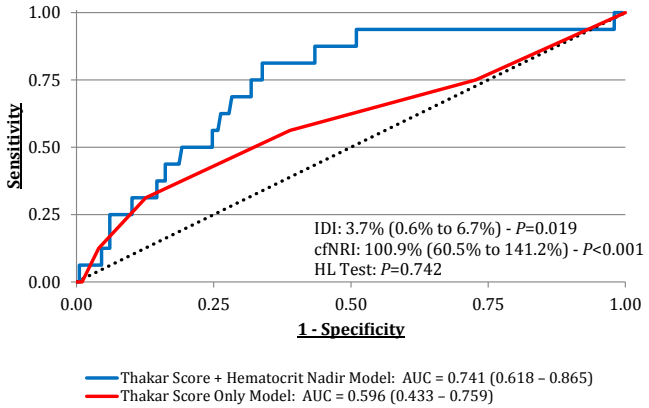

Figure 3. Comparison of receiver operator characteristic curves for the Cleveland Clinic (Thakar) score only and the Cleveland Clinic (Thakar) score + hematocrit nadir in the subset of patients without kidney dysfunction at baseline (n = 214). AUC, area under the curve; cfNRI, category-free net reclassification index; HL, Hosmer Lemeshow test; IDI, integrated discrimination improvement.

Importantly, nadir hematocrit improved discrimination significantly in this subcohort of patients without preexisting kidney disease, restoring discrimination of the model to a clinically adequate level and suggesting that measurement of nadir hematocrit might be especially useful in patients without CKD before surgery.

The mechanisms by which changes in hematocrit influence risk of AKI have not been fully elucidated.[18] Both direct and indirect effects have been suggested. It is plausible that a low hematocrit decreases oxygen delivery to the kidney, exacerbating renal hypoxia and contributing to injury.[43] Alternatively, hematocrit may be a marker for fluid shifts, hemodilution,[46] operative blood loss,[47] need for transfusions[48], or hemolysis,[19] each of which may influence the risk of ischemic and/or hypoxic renal injury. Because hemodilution and blood loss were indirectly evaluated by fluid balance and blood transfusion, respectively, and were not found to be significant, our results favor the hypothesis that hemolysis, with release of free hemoglobin, might be the key mediator of the relationship between hematocrit and AKI. Measurement of free hemoglobin perioperatively would have elucidated this possibility, but was not possible in this study. Finally, hematocrit and its correlates are potentially modifiable, and represent attractive targets for intervention in future trials of AKI prevention.

We did not find an association between mean intraoperative MAP and AKI, an observation congruent with several other studies. MAP measured in the OR may not adequately reflect organ perfusion, because most organs, including the kidney, possess a significant degree of autoregulation that maintains perfusion until perfusion pressure drops below some threshold. In the sensitivity analyses, we found that a threshold duration and severity of hypotension, defined as a sustained 25 minutes of MAP below 55 mm Hg, were associated with a statistically significant, albeit small, improvement in CSA-AKI prediction compared with the CCS alone. Although this finding is biologically plausible, it must be interpreted cautiously, as this observation was the result of a post hoc analysis involving multiple statistical tests. The risk of a spurious finding is therefore high. Moreover, several other studies have looked for and failed to find a similar blood pressure and/or duration threshold predictive of AKI.[43,49,50]

Volume of crystalloid input was not predictive of CSA-AKI in our study. Crystalloid volume plausibly contributes to hemodilution and may thus be confounded with and incorporated into the hematocrit effect. Alternatively, in our cohort of stable elective cardiac surgery patients, the observed variation in fluid administration between patients may have been too small to discern an impact on AKI risk. The difference in mean crystalloid administered to those who developed AKI and those who did not was less than 500 ml (Tables 4 and 5), which after redistribution would not cause large differences in intravascular volume or hematocrit. These same 2 reasons (i.e., confounding and lack of variation) could also explain why significant effects of blood transfusion on CSA-AKI were not observed in our study.

Our results have potential clinical and research implications. In the context of a growing body of literature highlighting the importance of intraoperative anemia, our findings support intraoperative monitoring of hematocrit, in addition to the CCS, as a feasible, useful, and economical way of improving risk prediction for AKI after surgery, particularly in patients without preexisting kidney disease. More accurate AKI risk classification during surgery could help inform subsequent care, in particular decisions regarding volume loading, diuretics, and transfusions in the immediate postoperative period. Identification of more targeted therapies for AKI prevention will rely in part on future elucidation of the main causal mechanisms underlying the association between low hematocrit and AKI. As discussed above, if the link is causal, aggressive correction of low hematocrit could improve risk AKI and clinical trials comparing higher versus lower transfusion thresholds based on nadir hematocrit will be needed to answer this question. On the other hand, if the link is mediated via the mechanism of hemolysis, as indirectly suggested by our data, then clinical trials of strategies to limit hemolysis or abrogate the toxic effects of free hemoglobin on the kidney should be prioritized.

Our study has several strengths. Our analysis prospectively examined intraoperative variables plausibly associated with renal ischemia reperfusion or hypoxia. Our main findings are biologically plausible, congruent with emerging literature, and can directly inform future research. Moreover, intraoperative hematocrit is easily and in some cases routinely measured, facilitating knowledge translation and clinical application.

Our study also has some limitations. The sample size was small and our study may have lacked the power to detect all associations between with intraoperative variables and AKI. Our study was not powered to examine hard outcomes such as dialysis or death. Finally, our study population comprised a relatively low risk cohort of elective cardiac surgery patients, with low to intermediate mean CCS. Generalizing our results to higher risk cardiac surgery patients may not be appropriate.

In conclusion, the addition of nadir hematocrit to a well-established preoperative risk score improved the prediction of AKI, especially in patients without preoperative kidney disease. In contrast, intraoperative MAP, crystalloid and blood product administration, and urine output did not improve the AKI prediction.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Sensitivity analysis comparing the impact of different thresholds for assessing changes in BP, hematocrit, fluid balance, and urine output on model discrimination.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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